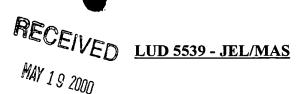
REMARKS

In response to the Examiner's remarks in Paragraph 2 of the Office Action, applicants submit concurrently herewith a CRF, a paper copy corresponding to the CRF, an amendment and a statement.

The Preliminary Amendment filed concurrently with this application is objected to under 35 U.S.C. § 132 for purportedly introducing new matter. The Examiner contends that the added material, i.e., the incorporation of the several U.S. and foreign priority applications, did not form part of the specification as filed. This application was filed with the Preliminary Amendment and without a signed Declaration. Applicants submit concurrently herewith a Declaration which refers to both the application and that Preliminary Amendment. Thus the Preliminary Amendment is considered a part of the original disclosure and does not introduce new matter (see MPEP § 608.04). In view of the forgoing applicants request that the Examiner reconsider and withdraw the objection.

The Examiner also contends that the Declaration is defective for purportedly failing to identify the specification to which it is directed. The Declaration submitted herewith identifies the application by its serial no. and filing date and as such complies with 37 C.F.R. § 1.67(a).

Claims 21-23 and 26 stand rejected under 35 U.S.C. § 102(b) for purportedly being anticipated by either Yingling et al. or Lechleider et al. In particular, the Examiner contends that each of the cited references describes the TGF-β induced phosphorylation of Smad-1 in a cellular system responsive to TGF-β, and each teaches that the latter species participates in signaling pathways in response to TGF-β. Applicants disagree.



Applicants have demonstrated that in the tabsence of ALK-1 Smad-1 is not phosphorylated in response to TGF-β (page 35, line 20 to page 36, line 10). ALK-1 is reported to be an endothelial cell type I receptor for the TGF-beta superfamily of ligands (See, e.g, Klaus et al., "Novel missense and frameshift mutations in the activin receptor-like kinase-1 gene in hereditary hemorrhagic telangiectasia" Hum Mutat 1998; 12 (2): 137, abstract). The cell lines used in Lechleider et al., i.e., A549 adenocarcinoma cells, are epithelial cells and the cells used in the experiments described in Yingling et al. are either epithelial cells (NmuMg) and myoblasts (L6)(page 8940). Without ALK-1 these cells would not phosphorylate Smad-1.

In addition, between the 1996 publication of Lechleider et al. and Yingling et al. and the 1998 filing date of this application, those of skill in the art came to the conclusion that Smads 1, 2, 3, and 5 were pathway restricted and that Smad-1 was restricted to the BMP signaling pathway and thus was <u>not</u> phosporylated in response to TGF-β (see the review article Heldin et al.,"TGF-β signaling from Cell Membrane to Nucleus Through SMAD Proteins" <u>Nature</u>, 390:465-471(1997) page 466, right col., last paragraph through page 467, left col.).

Applicants submit concurrently herewith a Declaration by Anita B. Roberts and Robert J. Lechleider (the Roberts and Lechleider Declaration), two authors of Lechleider et al.). Dr. Roberts and Dr. Lechleider state that in 1996 when Lechleider et al. and Yingling et al. were published, it was not known that other Smads existed. Thus in 1996 Dr. Roberts and Dr. Lechleider had assumed that the antiserum raised against a Smad-1 fusion was specific for Smad-1 and the phosphorylated protein they detected in response to treating cells with TGF-β was a phosphorylated Smad-1. Dr. Roberts and Dr. Lechleider now conclude that phosphorylated protein is not Smad-1.

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Drs. Roberts and Lechleider state that those of skill in the art came to appreciate that the antisera raised against Smad-1 fusion proteins which were used in their experiments were cross-reactive with the other Smads and based on the experiments conducted between 1996 and 1998, which were designed to analyze the role of the SMADs in signaling pathways, they and others of skill in the art believed that Smads 1, 2, 3, and 5 were pathway restricted: Smad-1 being restricted to the BMP signaling pathway and not phosporylated in response to TGF-β (see, e.g., the review article Heldin et al., Nature 390: 465-71 (1997) page 267, left col.). Heldin et al., demonstrates that in 1997 those of skill in the art understood that the different members of the SMAD family had different roles in signaling and acted in a pathway restricted manner (see Heldin et al., Table 1, and page 466, right col. last paragraph to page 447, left col.). The pathway restricted Smads coupled with different receptors, e.g., Smad-2 and Smad-3 were phosphorylated and translocated after stimulation with TGF-β, while Smad-1 was phosphorylated and translocated only in response to stimulation by BMP-2 or BMP-4 (Heldin et al., page 466, right col. last paragraph to page 447, left col.). Based on this information Dr. Roberts and Lechleider concluded that the phosphorylated protein detected by Lechleider et al. was not Smad-1 but rather other phosphorylated Smads.

Thus, neither Lechleider et al. or Yingling et al., alone or in combination, teach that Smad-1 is phosphorylated in response to TGF-β. Therefor, Lechleider et al. and Yingling et al. fail to anticipate applicants' invention as claimed.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102.

Claim 24 stands rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over either one of Yingling et al. or Leichleider et al.. The Examiner contends that it would have been obvious to use a fragment of TGF-β, which the Examiner contends was known or

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was reasonably expected to be capable of signaling in the same manner as native TGF- β , in the method of Yingling et al. or Leichleider et al. Applicants disagree. The cited art does not provide the motivation or the expectation of success necessary to render applicants' claims obvious.

"[A] proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . . Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." <u>In re Vaeck</u>, 20 U.S.P.Q.2d 1438, 1442 (C.A.F.C. 1991)

"Although couched in terms of combining teachings found in the prior art, the same inquiry must be carried out in the context of a purported obvious "modification" of the prior art. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (C.A.F.C. 1992)

As applicants have discussed *supra*, at the time of filing, those of skill in the art believed that the phosphorylated proteins disclosed in Yingling et al. and Leichleider et al. were misidentified and were <u>not Smad 1</u> but were instead were other phosphorylated Smads. The review article, Heldin et al., <u>Nature 390: 465-71 (1997)</u> demonstrates that in 1997 those of skill in the art understood that the different members of the SMAD family had different roles in signaling and acted in a pathway restricted manner (see Table 1, and page 466, right col. last paragraph to page 447, left col.). The ordinary skilled worker believed that the

pathway restricted Smads coupled with different receptors and that it was Smad-2 and Smad-3 that were phosphorylated and translocated after stimulation with TGF- β , while Smad-1 was phosphorylated and translocated only in response to stimulation by BMP-2 or BMP-4 (Heldin et al., page 466, right col. last paragraph to page 447, left col.). Thus prior to applicants' disclosure there was no motivation to enhance the expression of a gene that is activated by phosphorylated Smad-1 by contacting cells with TGF- β , or a fragment thereof, and one of skill in the art at the time of this invention would not have expected that exposure to TGF- β would result in Smad-1 phosphorylation or enhance the expression of a gene that is activated by phosphorylated Smad-1. As such, Yingling et al. and Leichleider et al. fail to render applicants' invention obvious. In view of the foregoing remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim 28 stands rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over either one of Yingling et al. or Leichleider et al. as taken in view of Basson et al. As discussed *supra*, those of skill in the art believed that Yingling et al. and Leichleider et al. had misidentified the proteins phosphorylated in their assays. At the filing date of this application those of skill in the art believed that Smad-1 interacted with, and was phosphorylated only in response to, BMPs and thus that Leichleider et al. and Yingling et al. had misidentified the phosphorylated protein as Smad-1. Applicants' are the first to demonstrate that Smad-1 was phosphorylated by ALK-1 in response to exposure to TGF-β. Thus, even if Basson et al. suggest probing signaling pathways by isolating and identifying mRNA transcripts that are present at elevated levels in response to signaling species, there was no motivation prior to applicants' disclosure to inhibit or activate Smad-1 phosphorylation with TGF-β. Therefore, Leichleider et al. and Yingling et al. alone or in combination with Basson et al. fail to teach or suggest applicants' claims. In view of the

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foregoing remarks applicants request that the Examiner reconsider and withdraw the rejection.

The Commissioner is hereby authorized to deduct any missing or insufficient fee from deposit account 500624.

Respectfully submitted,

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